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Treatment of High-Risk Acute Lymphoblastic Leukemia in Children Using the AL851 and ALHR88 Protocols: A Report From the Kyushu-Yamaguchi Children's Cancer Study Group in Japan

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A total of 125 children, who were diagnosed as having high-risk acute lymphoblastic leukemia (ALL), were treated with two consecutive protocols designated as AL851 (1985–1988) and ALHR88 (1988–1990). All patients received induction therapy consisting of vincristine (VCR), prednisolone (PSL), daunorubicin (DNR), and l-asparaginase (l-Asp). In the ALHR88 protocol, the patients whose blasts in the bone marrow (BM) were ≥25% on day 14 of induction therapy and who were classified into T-cell type received additional cytosine arabinoside (AraC). After consolidation with intermediate-dose methotrexate (MTX), reinduction therapy including VCR, dexamethasone, and adriamycin followed by high-dose AraC was done for all patients. Intrathecal MTX and 24Gy of cranial irradiation were used to prevent central nervous system leukemia. A maintenance therapy consisting of 6-mercaptopurine, cyclophosphamide, MTX, DNR, VCR, and AraC was administered for 3 years after achieving a complete remission (CR). CR was achieved in 51/55 (92.7%) for AL851 and 68/70 (97.1%) for ALHR88. The 5-year event-free survival rates were 49.1 ± 6.7% in AL851 and 62.5 ± 6.1% in ALHR88. The factors related to a poor prognosis were a high initial leukocyte count of greater than 50×10^9/L ($P < 0.001$), an L2 morphology of leukemic cells by FAB classification ($P = 0.009$), the chromosomal abnormality ($P = 0.004$) and high residual leukemic cells in BM (≥25%) on day 14 of induction therapy ($P < 0.001$). Taking these factors into consideration, more intensive protocols were started in 1990 for the patients with high-risk ALL.

Key words: ALL, chemotherapy, high-risk group, children

INTRODUCTION

The long-term survival rate, or possible cure rate, in children with acute lymphoblastic leukemia (ALL) has reached approximately 60–70% over the past 10 years [1–3]. However, the outcome of patients with several prognostic characteristics such as a high leukocyte count, young age (less than 2 years) or older age (more than 10 years), and organomegaly remains unfavorable [1–3]. For the improvement of these patients' prognoses, different therapeutic strategies should be designed on the basis of the relative risk in the treatment failure.

The Kyushu-Yamaguchi Children's Cancer Study Group was organized as the multicenter therapeutic trial in the southern part of Japan, and the first protocol for high-risk ALL, AL851, was started in 1985. The notable feature of this protocol was an early intensive multiagent chemotherapy consisting of induction, consolidation, and reinduction therapy conducted over the first 6-month period. Remission induction consisted of a four-drug combination of vincristine (VCR), prednisolone (PSL), l-asparaginase (l-Asp), and daunorubicin (DNR). Rein-

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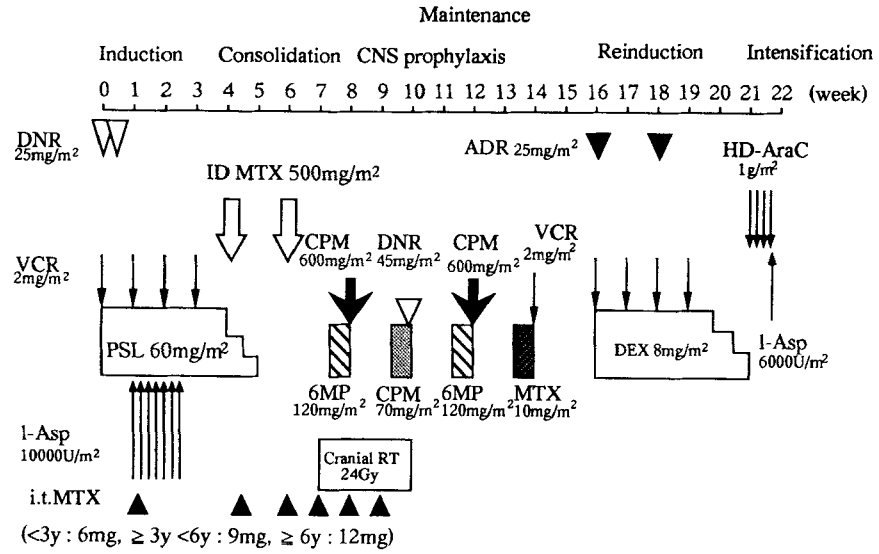
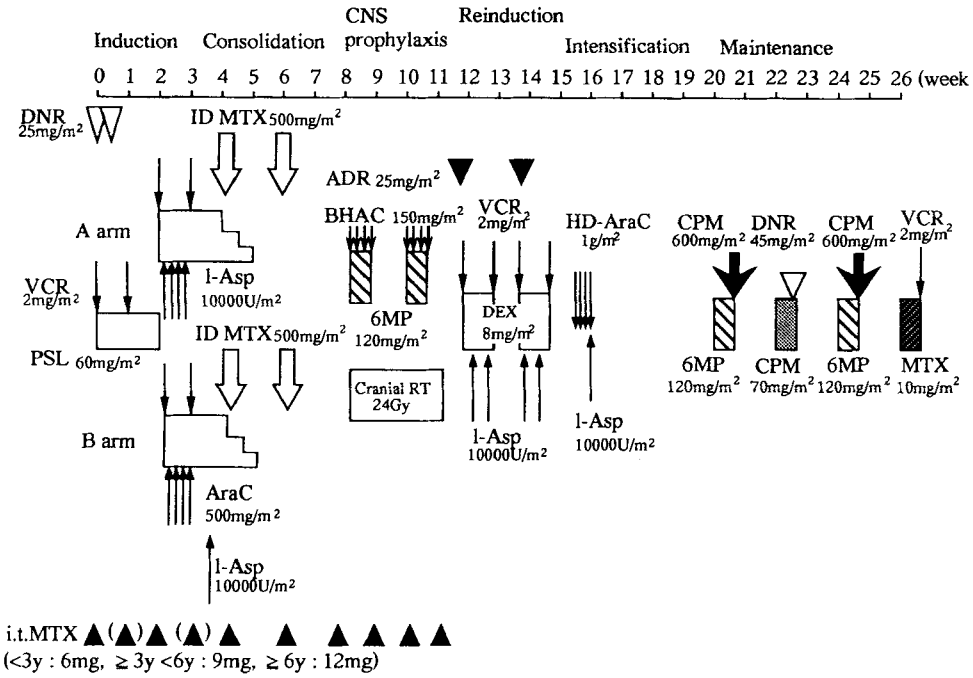


Protocol AL851



Protocol ALHR88

Fig. 1. Schematic presentation of protocol AL851 and ALHR88. The precise schedule of administration is described in the text. In induction therapy of ALHR88, IT-MTX was additionally administered at the days noted in parenthesis when CNS involvement existed at the time of diagnosis. Leucovorin (12 mg/m^2, IV, or PO) was given at 18 and 24 hours after MTX administration in the consolidation. AraC (200 mg/m^2) replaced DNR when the total dose of DNR reached 450 mg/m^2. Total dose of administered anthracyclines (DNR and ADR) was 500 mg/m^2. VCR, vincristine; DNR, daunorubicin; l-Asp, l-asparaginase; PSL, prednisolone; MTX, methotrexate; AraC, cytosine arabinoside; BHAC, enocitabine; 6MP, 6-mercaptopurine; CPM, cyclophosphamide; ADR, adriamycin; DEX, dexamethasone.

duction therapy using VCR, dexamethasone (DEX), adriamycin (ADR), and high-dose cytosine arabinoside (HD-AraC) followed consolidation with an intermediate-dose of methotrexate (ID-MTX) to prevent a relapse in the early phase after achieving remission. A cranial irradiation of 24Gy with intrathecal MTX administrations was applied for the prophylaxis of central nervous system (CNS) leukemia. For the maintenance therapy, six drugs were biweekly administered either intravenously or orally for 3 years, according to the modified LSA_2L_2 protocol [4]. A preliminary analysis of the treatment results with AL851 resulted in some modifications of the protocol, and thus the second trial ALHR88 was started in 1988. We herein report the treatment results of the two successive AL851 and ALHR88 protocols for high-risk ALL in children.

PATIENTS AND METHODS

Patients

From April 1985 to July 1990, a total of 125 untreated high-risk ALL patients younger than 16 years of age were enrolled into the two consecutive protocols consisting of AL851 (from April 1985 to June 1988) and ALHR88 (from July 1988 to July 1990) from the 14 member institutions of the group (see Appendix). The final diagnoses of ALL for all patients were made at the National Kyushu Cancer Center based on the morphological and immunochemical evaluation of bone marrow (BM) samples. High-risk ALL was defined as patients who showed at least one of the following clinical findings: 1) a white blood cell (WBC) count at diagnosis was $\geq 25 \times 10^9$/L; 2) an age at diagnosis of <2 years or ≥ 8 years for boys, and <2 years and ≥ 10 years for girls; 3) an enlargement of the liver, spleen (≥ 5 cm under the costal margin) and/or lymph node (≥ 5 cm in diameter). Any patients with a mature B-cell phenotype and/or FAB L3 morphology were excluded from the study. In the ALHR88 protocol, all patients whose leukemic cells had a T-cell phenotype were entered into the study.

Treatment Protocol

The two therapeutic protocols are summarized in Figure 1. Protocol AL851 included an induction therapy consisting of PSL, VCR, DNR, l-Asp, and intrathecal MTX (IT-MTX) for 4 weeks. The patients, who did not achieve complete remission (CR) after the 4-week induction therapy, received PSL and VCR for additional 2 weeks. Those who did not attain a CR after the 6-week induction therapy did not continue the therapy regimen. Consolidation therapy included intermediate-dose MTX (ID-MTX) and IT-MTX at 2-week intervals. All patients received 24 Gy of cranial irradiation and six doses of IT-MTX for CNS leukemia prophylaxis. In the meantime, one cycle of maintenance therapy was prescribed for these patients. The maintenance therapy consisted of the oral administration of either 6-mercaptopurine (6MP), CPM or MTX for 4 days, and the intravenous administration of either CPM, DNR, AraC, or VCR. After the first cycle of maintenance, patients received reinduction therapy consisting of DEX, VCR, and ADR for 4 weeks followed by an intensification therapy containing HD-AraC (4 times every 12 hours) and l-Asp. Following the treatment with HD-AraC, the maintenance therapy resumed and continued for 3 years after achieving a CR.

The ALHR88 protocol was designed in 1988 to prevent both induction failure and an early relapse. All patients received PSL, VCR, DNR, and IT-MTX during the first two weeks. BM aspiration was done for all patients on day 14 of induction therapy to examine the number of residual leukemic cells. The patients, who showed $\geq 25\%$ blasts in BM on day 14 or who had T-cell ALL, received PSL, VCR, AraC, l-Asp, and IT-MTX over the next 2 weeks (B arm), while the others received PSL, VCR, l-Asp, and IT-MTX (A arm). The patients who did not attain CR on day 28 then received PSL and VCR for 2 more weeks, while those who failed to achieve CR after the therapy were removed from the protocol. Following the induction therapy, the patients received consolidation therapy with ID-MTX and CNS leukemia prophylaxis with IT-MTX and 24 Gy of cranial irradiation. Systemic chemotherapy including enocitabine (BHAC) and 6MP was added during the CNS prophylaxis. Reinduction therapy with ALHR88 began about 4 weeks earlier than that with AL851. The duration of DEX administration was reduced to 14 days at 7-day intervals, and l-Asp was also added. Maintenance therapy continued for 36 months after achieving a CR.

During maintenance therapy, all patients received BM examination every 2 months and cerebrospinal fluid examination every 4 months. Testicular biopsy was done on all males treated with either AL851 or ALHR88 at the end of therapy.

Definitions of Response

M1 marrow was defined as a BM containing blasts, including both normal and leukemic blasts, equal to or less than 5% of all nucleated cells. A CR was defined as a state with a normal peripheral blood count, M1 marrow, normal cerebrospinal fluid morphology, and no abnormal physical findings attributable to leukemia. A diagnosis of bone marrow relapse was made when the lymphoblasts comprised $\geq 25\%$ of the BM.

Statistical Analysis

The duration of event-free survival (EFS) was defined as the interval between the diagnosis of ALL and the occurrence of the event or the most recent follow-up. The notable events considered were induction failures (a failure to achieve a CR and death during the induction therapy), death during CR, and relapse. The EFS rates were estimated with

TABLE I. Characteristics of Patients of High-Risk ALL Treated With Either AL851 or ALHR88

Characteristics	AL851	ALHR88 Total	ALHR88 Arm (A)	ALHR88 Arm (B)
No. of patients	55	70	(56)	(14)
Sex				
Male	35	36	(27)	(9)
Female	20	34	(29)	(5)
Age (year)				
Male				
<1	3	1	(1)	(0)
≥1– <2	1	5	(5)	(0)
≥2– <8	12	16	(10)	(6)
≥8– <16	19	14	(11)	(3)
Female				
<1	3	0	(0)	(0)
≥1– <2	5	3	(3)	(0)
≥2– <10	4	19	(16)	(3)
≥10– <16	8	12	(10)	(2)
WBC ($\times 10^9$/L)				
<10	18	27	(21)	(6)
≥10– <50	19	25	(23)	(2)
≥50– <100	10	6	(5)	(1)
≥100	8	12	(7)	(5)
Hb (g/dl)				
<10	39	53	(45)	(8)
≥10	16	17	(11)	(6)
Platelet ($\times 10^9$/L)				
<100	29	52	(44)	(8)
≥100	26	18	(12)	(6)
FAB classification				
L1	34	50	(41)	(9)
L2	20	20	(15)	(5)
Unknown	1	0		
Surface phenotype[a]				
Null	11	12	(8)	(4)
Common	30	41	(37)	(4)
PreB	0	6	(6)	(0)
T	8	6	(1)[b]	(5)
Unknown	6	5	(4)	(1)
Organ involvement				
Liver (≥5 cm)	16	24	(19)	(5)
Spleen (≥5 cm)	10	21	(16)	(5)
Lymph node (≥5 cm)	3	4	(2)	(2)
CNS	ND[c]	2	(1)	(1)
Others	2[d]	0		
Karyotype[e]				
Hypodiploid (<46 chromosomes)	0	2	(1)	(1)
Diploid	19	29	(23)	(6)
Pseudodiploid (46 chromosomes with abnormalities)	4	14	(11)	(3)
Hyperdiploid (47 to 50 chromosomes)	0	2	(2)	(0)
Hyperdiploid (≥50 chromosomes)	0	3	(3)	(0)
ND or unknown	32	20	(16)	(4)

[a]Null, HLA-DR+, CD19+/−, CD10−; Common, HLA-DR+, CD19+, CD10+, CD20+/−; PreB, cytoplasmic immunoglobulin +.

[b]Treated with A arm by mistake because CR was obtained on day 14 of induction. He continued CR afterward.

[c]ND, not determined because the cerebrospinal fluid was not examined at diagnosis in AL851.

[d]Included involvement of the kidney and skin.

[e]Karyotypes were analyzed at different laboratories. Pseudodiploid included t(9;22) in three patients, t(1;19) in two, and t(8;14) in one.

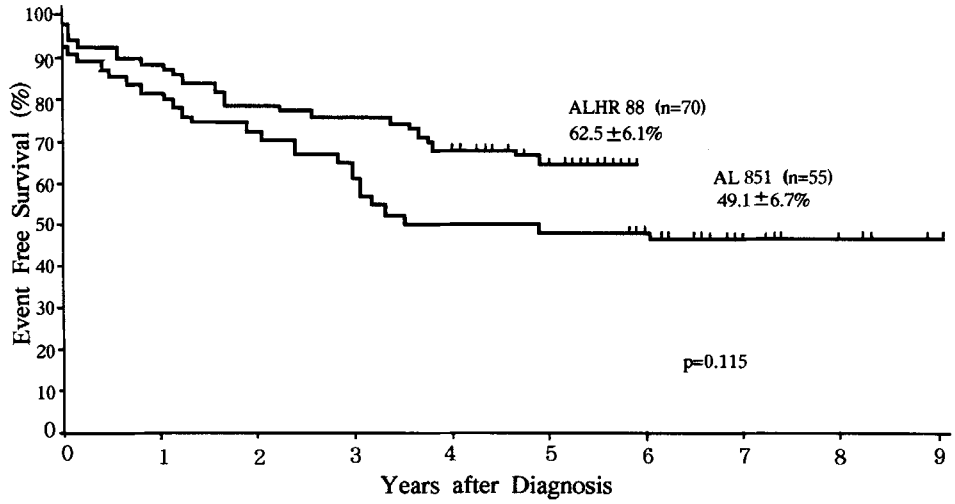


Fig. 2. A Kaplan-Meier plot of probability of the event-free survival rates in patients treated with either AL851 or ALHR88.

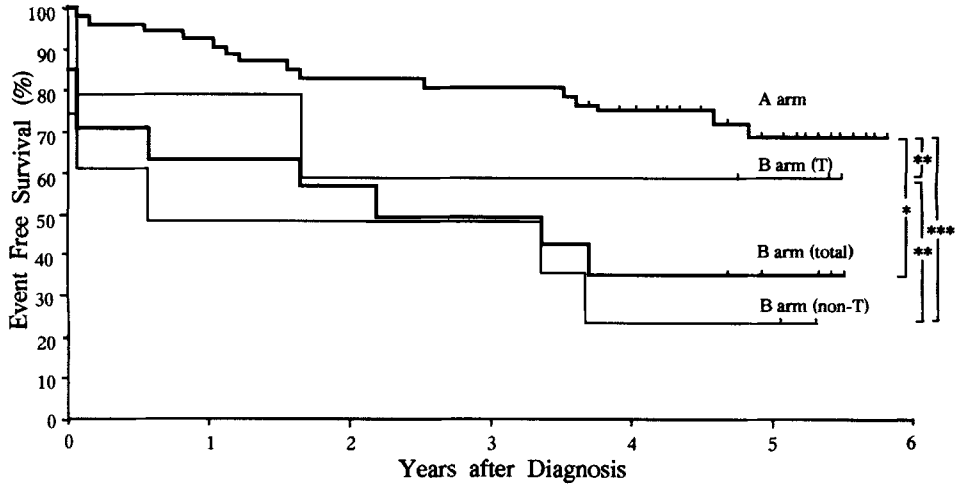


Fig. 3. The event-free survival (EFS) rates of patients treated with either the A arm or B arm of ALHR88, and those of patients subdivided into either the T group or the non-T group of the B arm. The 5-year EFS rates were: A arm (n = 56): 68.9 ± 6.7%; B arm (total, n = 14) 35.7 ± 12.8%; B arm (T group, n = 5): 60.0 ± 21.9%; and B arm (non-T group, n = 9): 25.0 ± 15.3%. *, $P = 0.039$; **, not significant; ***, $P < 0.001$.

the use of Kaplan-Meier method [5], and those in the two groups were compared with the use of the log-rank test [6] or Cox's proportional hazard regression model [7]. An induction failure was considered as a event of day 0. Comparisons of the frequency of both clinical and laboratory features between two groups were performed with the chi-square test [8]. The analysis was done according to the treatment results as of April 30, 1994.

RESULTS

Patient Characteristics

Table I shows the clinical and laboratory findings at the initial presentation of 125 patients who were enrolled in the studies. The median age of the patients entered into the AL851 and ALHR88 protocols was 7.6 years and 7.2 years, respectively. Characteristics which showed statistical difference in distribution of the patients between the two protocols were age, platelet count, and surface phenotype. The number of patients in AL851 with ages of <2 or ≥ 8 years in male and <2 or ≥ 10 years in female was larger than that in ALHR88 ($P = 0.029$). AL851 especially included six infant ALL with <1 year of age ($P = 0.043$). The number of patients with platelet count of $<100 \times 10^9$ in ALHR88 was larger than that in AL851 ($P = 0.021$). There was no patient with preB ALL in AL851 ($P = 0.036$). The follow-up periods ranged from 72 to 110 months (median 87 months) for

TABLE II. The Outcome of Patients Treated With Either AL851 or ALHR88*

	AL851	ALHR88		
		Total	A	B
No. of patients	55	70	56	14
Complete remission	51	68	56	12
(%)	(92.7)	(97.1)	(100)	(85.7)
Relapses				
BM	15	13	7	6
CNS	3	1	1	0
Testis	5	0	0	0
LN	0	1	1	0
Skin	0	1	1	0
BM+CNS	0	1	1	0
BM+testis	1	0	0	0
BM+skin	0	1	0	1
CNS+testis	1	0	0	0
Total	25	18	11	7
Development of MDS	0	1	1	0
Death				
After relapse	17	10	6	4
In CCR	0	4[a]	4	0
EFS (%)				
3-year	61.8 ± 6.6	74.3 ± 5.2	80.4 ± 5.3	50.0 ± 13.4
5-year	49.1 ± 6.7	62.5 ± 6.1	68.9 ± 6.7	35.7 ± 12.8
9-year	47.1 ± 6.8	—	—	—
Outcome after relapse or development of MDS				
Survival	8	9	6	3
BMT allogenic	4	3	1	2
autologous	1	1	1	0

*BM, bone marrow; CNS, central nervous system; LN, lymph node; MDS, myelodysplastic syndrome; CCR, continuous complete remission; EFS, event free survival; BMT, bone marrow transplantation.
[a]Three patients died from infection and one from a traffic accident.

AL851 and from 46 to 72 months (median 59 months) for ALHR88.

Outcome of the Treatments

The treatment outcome is summarized in Table II. Fifty-one of the 55 patients (92.7%) treated with AL851 and 68 of the 70 patients (97.1%) treated with ALHR88 achieved a CR. Five in AL851 and two in ALHR88 needed 6 weeks for achieving CR. Five of six patients with induction failure died from sepsis (three in AL851 and one in ALHR88) and acute renal failure (one in AL851). Another patient achieved a CR using a different induction therapy.

Twenty-five of the 51 patients in AL851 (49.0%) and 18 of the 68 patients in ALHR88 (26.5%) relapsed. In AL851, the relapse occurred during the chemotherapy in 19 and, particularly, 10 relapsed within 18 months after the beginning of therapy. In ALHR88, 13 patients relapsed during chemotherapy and eight relapses occurred within 18 months. Of seven patients needing 6-week induction therapy, four (2/5 in AL851 and 2/2 in ALHR88) relapsed. One notable feature was a high incidence of isolated testicular relapse in five patients with AL851 (14.3% of boys); two with overt testicular relapse during maintenance therapy (15 and 23 months after beginning therapy) and three with testicular infiltration detected by a testicular biopsy at the end of the therapy. One patient treated with ALHR88 developed myelodysplastic syndrome 47 months after the beginning of treatment. The estimated 5-year EFS rates were 49.1 ± 6.7% in AL851 and 62.5 ± 6.1% in ALHR88 (Fig. 2). The EFS improved in ALHR88, but it did not reach statistical significance ($P = 0.115$). The 5-year EFS rates, when excluding infant ALL, were 49.0 ± 7.2% in AL851 and 63.4 ± 6.1% in ALHR88 ($P = 0.107$). In ALHR88, the 5-year EFS rate in patients in the B arm was significantly lower than that in the A arm (Fig. 3, $P = 0.039$).

Analysis of Prognostic Factors

Various potential prognostic factors in this study were analyzed and are shown in Table III. WBC count at diagnosis, FAB classification of leukemic cells and chromosomal abnormality were significant predictors of outcome. Of three patients with t (9;12), one in AL851 failed to achieve CR, and the other two, treated with either AL851 or ALHR88, relapsed 16 and 19 months after the beginning of therapy. In AL851, the EFS rate in patients with a low platelet count ($<100 \times 10^9$/L) was significantly lower than that with a normal platelet count ($P = 0.035$).

TABLE III. Prognostic Factors in Patients Treated With Either AL851 or ALHR88*

Characteristics	5-year EFS (mean ± SE), *P*-value (log-rank test)					
	Total		AL851		ALHR88	
Sex						
Male	55.2 ± 5.9		41.7 ± 8.2		68.2 ± 8.1	
Female	59.2 ± 6.9	n.s.	63.2 ± 11.1	n.s.	57.0 ± 9.0	n.s.
Age (year)						
<2	50.0 ± 11.2		45.5 ± 15.0		55.6 ± 16.6	
≥2– <10	56.8 ± 7.1		35.1 ± 10.5		67.3 ± 7.9	
≥10	59.3 ± 6.9	n.s.	59.1 ± 10.5	n.s.	59.3 ± 10.7	n.s.
WBC ($\times 10^9$/L)						
<50	68.0 ± 5.1		61.8 ± 8.1		69.6 ± 6.8	
≥50	30.0 ± 7.8	<0.001	16.7 ± 8.8	<0.001	42.9 ± 12.1	0.035
Hb (g/dl)						
<10	57.9 ± 5.3		51.3 ± 8.0		63.0 ± 6.9	
≥10	54.0 ± 8.8	n.s.	43.8 ± 12.4	n.s.	62.8 ± 12.3	n.s.
Platelet ($\times 10^9$/L)						
<100	53.1 ± 5.9		35.7 ± 9.1		63.0 ± 6.6	
≥100	62.2 ± 7.2	n.s.	63.0 ± 9.3	0.035	61.1 ± 11.5	n.s.
FAB classification						
L1	65.0 ± 5.3		58.8 ± 8.4		68.4 ± 7.0	
L2	41.4 ± 8.0	0.009	35.0 ± 10.4	n.s.	48.1 ± 11.7	n.s.
Surface phenotype						
Null	56.5 ± 10.3		63.6 ± 14.5		50.0 ± 14.4	
Common	55.8 ± 6.2		43.3 ± 9.1		64.4 ± 7.0	
PreB	66.7 ± 19.3		—		66.7 ± 19.3	
T	57.1 ± 13.2	n.s.	50.0 ± 17.7	n.s.	66.7 ± 19.3	n.s.
Karyotype						
Normal	68.8 ± 6.7		57.9 ± 11.3		75.9 ± 8.0	
Abnormal	33.3 ± 10.2	0.004	0 ± 0	<0.001	39.7 ± 11.6	0.019
Organ involvement						
Negative	58.0 ± 5.7		44.4 ± 8.3		70.7 ± 7.1	
Positive	54.5 ± 7.5	n.s.	52.1 ± 11.6	n.s.	48.9 ± 10.9	n.s.

*n.s., not significant. The number of patients in each group is shown in Table I.

TABLE IV. Initial Clinical and Laboratory Characteristics Related to the Improvement of the EFS Rate in ALHR88

Characteristics	5-year EFS (%)		*P*-value	
	AL851	ALHR88	Univariate[a]	Multivariate[b]
Sex				
Male	41.7 ± 8.2	68.2 ± 8.1	0.026	0.004
WBC				
≥50 × 10^9/L	16.7 ± 8.8	42.9 ± 12.1	0.059	0.018
Platelet				
<100 × 10^9/L	35.7 ± 9.1	63.0 ± 6.6	0.022	0.030
Surface phenotype				
Common	43.3 ± 9.1	64.4 ± 7.0	0.073	0.084

[a]Analyzed by log-rank test.
[b]Analyzed by Cox's proportional hazards model.

The initial clinical and laboratory characteristics which may be related to the improvement of the EFS rate in ALHR88 were sex, WBC count, and platelet count (Table IV).

Despite the more intensive induction therapy, the EFS rate in patients treated with the B arm of ALHR88 was significantly lower than that of the A arm ($P = 0.039$, Fig. 3). No clinical or laboratory characteristics at diagnosis were able to help predict the arms to which the patients belonged (data not shown).

To elucidate the potential factors to influence the prognosis, the patients in the B arm were subclassified into two groups; the patients with T-cell ALL (T group) and others (patients with ≥25% blasts in BM on day 14, non-T group). The characteristics of the patients at diagnosis showed no statistical difference between these two

groups. The 5-year EFS rates of the T group and the non-T group were 60.1 ± 21.9% and 25.0 ± 15.3%, respectively, with no statistical difference ($P = 0.269$, Fig. 3). However, when the outcome of each group in the B arm was compared with that in the A arm, the EFS rates of non-T group was significantly lower than that of patients with the A arm ($P < 0.001$) while the outcome of the T group was almost the same as the A arm. These results suggested that the BM finding on day 14 was thus an important factor in predicting the treatment results.

Toxicity

Seven patients died of either septicemia or pneumonia due to severe myelosuppression; during induction therapy in four patients, early after a CR in two, or during maintenance therapy in one. The severe side effects which caused the cessation of the administration of drugs included hyperglycemia due to l-Asp in three patients or due to PSL in one, myocardial insufficiency due to DNR in two, acute pancreatitis due to l-Asp in one, severe stomatitis due to MTX in one, convulsion due to AraC in one, and cataracts due to PSL in one. The VCR dose was reduced in two patients because of severe peripheral neuropathy. Frequently observed complications included mucositis in 12.5% of the patients and liver dysfunction (>500IU/L of transaminase) in 20.8% due to MTX. In two patients, liver dysfunction caused by 6MP was also observed. Other documented complications were hemorrhagic cystitis due to CPM, ileus, and an inappropriate secretion of antidiuretic hormone due to VCR, peptic ulcer and psychosis due to DEX. However, these side effects were only transient and recovered by the cessation or modification of chemotherapy.

DISCUSSION

The patients with high-risk ALL, who were selected on age, sex, leukocyte count, degree of organ involvement, and surface phenotype, were treated with two consecutive protocols. In AL851, all patients received the same combination chemotherapy. In ALHR88, the patients were divided into two groups according to the BM finding on day 14 and immunophenotype of leukemic cells, and those with residual leukemia and/or T-cell ALL received more intensive induction therapy including AraC. In addition, the reinduction therapy of ALHR88 was started 4 weeks earlier than that of AL851 to prevent an early relapse.

The remission induction rates of AL851 and ALHR88 were 92.7% and 97.1%, respectively. The CR rates obtained are almost the same as those in other study groups using the four-drug combination of VCR, PSL, l-Asp, and anthracyclines [3]. The 25 of 51 patients in AL851 and 18 of 68 patients in ALHR88 relapsed, and the 5-year EFS rates of AL851 and ALHR88 were 49.1 ± 6.7% and 62.5 ± 6.1%, respectively. The EFS in ALHR88 is almost identical to the other results for high-risk ALL; 65–70% in BFM study group [9], 60% in CCSG [10], and 69% in a St. Jude study [11], although it is difficult to compare the results directly with those from other study groups because each therapeutic trial has used different criteria for patient stratification [1–3].

The present study revealed that the initial laboratory findings such as a high WBC count greater than 50×10^9/L, L2 morphology, and chromosomal abnormality were related to an unfavorable prognosis. A low platelet count less than 100×10^9/L was also associated with a poor prognosis in AL851. All of these factors have been reported to be associated with a poor prognosis [1–3,12]. However, the EFS of patients with low platelet count significantly improved in ALHR88 and then its prognostic value was lost. On the other hand, the initial WBC count remained a risk factor although the treatment outcome also improved in patients with a WBC count greater than 50×10^9/L. Patients with a high initial WBC count ($>50 \times 10^9$/L) are generally recognized as having a particularly poor prognosis [13]. Several investigators have demonstrated a close association between the L2 morphology and a poor prognosis [12,14,15], while some other reports did not [16,17]. A chromosomal abnormality of leukemic cells could influence the treatment outcome in ALL [1–3]. Patients with hyperdiploid ALL have a good prognosis [18,19], whereas those with near-haploid ALL have a very high risk of early relapse [20,21]. In our study, we could not evaluate the influence of each chromosomal abnormality to the treatment outcome because of the small number of patients with each abnormality.

The results of ALHR88 revealed that the BM finding on day 14 had a prognostic value. The EFS of the patients with ≥25% blasts in BM on day 14 was significantly lower than that in the others with a successful cytoreduction even though an intermediate-dose of AraC was added to intensify the treatment for these patients. Recent studies have indicated that residual leukemia in BM on day 14 of the induction phase is an important independent predictor of outcome [12,22,23]. Thus, a more intensive induction and consolidation chemotherapy should be applied for these patients.

The immunophenotype did not appear to correlate with prognosis in the present study. Although T-cell ALL has been reported to be associated with a poor prognosis in many studies [3], several studies have demonstrated that the prognostic influence of the T-cell phenotype will be lost when patients are treated with very intensive protocols [9,12].

The high incidence of testicular relapse was observed in patients treated with AL851, whereas there was no testicular relapse in ALHR88 ($P = 0.025$). Although the reason is unclear, the lack of any testicular relapse in

ALHR88 may be one of the responsible factors for the improvement of EFS. Some previous studies reported that the dose of MTX was associated with the prevention of testicular relapse [2,24,25], but in this study the dose of MTX was identical in the two protocols. The early application of the reinduction therapy in ALHR88 might be also responsible for the improvement in the results. To confirm this possibility, results should be analyzed in randomized trials in which reinduction therapy is applied with different timing.

The results of the present protocols were almost the same as those of the current reports of international studies [2,24]. Although the EFS of ALHR88 tended to improve when compared with that of AL851, we could not exclude the possibility that the results might be attributable to changes in supportive care rather than anti-leukemic therapy. In order to obtain further improvement in the prognosis of high risk ALL, each patient should be properly classified into several subgroups according to the prognostic factors, and thereafter treated with the optimal therapy including randomization.

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APPENDIX. Participating Principal Investigators in the Kyushu-Yamaguchi Children's Cancer Study Group

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Fukuoka University	Pediatrics	K Nibu, MD, F Yanai, MD
	Pathology	M Kikuchi, MD, M Takeshita, MD, K Ohshima, MD
	Radiology	K Jingu, MD
Hamanomachi Hospital	Pediatrics	T Inamitsu, MD, H Nakayama, MD, K Honda, MD
Kagoshima City Hospital	Pediatrics	H Take, MD, T Kai, MD
Kitakyushu City Yahata Hospital	Pediatrics	K Ichikawa, MD
Kitakyushu Municipal Medical Center	Pediatrics	Y Yoshida, MD, M Hirosawa, MD
Kokura National Hospital	Pediatrics	M Mukuno, MD, H Morita, MD
Kyushu University	Pediatrics	K Ueda, MD, A Matsuzaki, MD, S Ohga, MD
	Pediatric Surgery	S Suita, MD, Y Zaizen, MD
	Radiology	S Uehara, MD
Kyushu Welfare Pension Hospital	Pediatrics	K Joh-o, MD, Y Sakaguchi, MD
Kurume University	Pediatrics	H Eguchi, MD, H Inada, MD
	Radiology	N Hayabuchi, MD
Miyazaki Medical College	Pediatrics	T Sugimoto, MD, M Moriya, MD
Miyazaki Prefectural Hospital	Pediatrics	K Miyake, MD
Nakatsu National Hospital	Pediatrics	C Tsuboi, MD
National Beppu Hospital	Pediatrics	J Kukita, MD
Oita Medical University	Pediatrics	T Ishihara, MD, S Suenobu, MD
Oita Prefectural Hospital	Pediatrics	T Inoue, MD, Y Tamai, MD
Oita Red Cross Hospital	Pediatrics	H Shin, MD
Saga Medical School	Pediatrics	S Miyazaki, MD, N Yoshida, MD, H Koga, MD
Saga Prefectural Hospital Koseikan	Pediatrics	E Ishii, MD
Tokuyama Central Hospital	Pediatrics	K Fujita, MD
Tsushima Izuhara Hospital	Pediatrics	M Ito, MD
University of Occupational and Environmental Health	Clinical Epidemiology	M Ikeda, MD
Yamaguchi University	Pediatrics	M Koga, MD, K Kawasaki, MD, Y Umemoto, MD